Human Plasma Metabolites Associated with Established AMD Risk Genes

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Summary

• AMD risk SNPs have an impact on the plasma metabolome.
• Genetic-metabolomic associations can provide unique insights into the pathogenesis of AMD.
• Highest number of associations were seen with LIPC polymorphisms, which were associated with glycerophospholipid metabolites.
• LIPC gene and glycerophospholipid pathway are likely crucial in AMD pathogenesis and may represent potential targets for treatment of AMD.
AMD

Environmental risk factors

Genetic risk factors

Functional consequences?

34 loci

>7,000 SNPs
(single nucleotide polymorphisms)

AMD

Genetic

Metabolites
Goal

To analyze **associations between known AMD risk SNPs and plasma metabolites** in a cohort of AMD patients and controls
Methods

Boston, US
n = 191 fasting plasma samples

Coimbra, Portugal
n = 295 fasting plasma samples

Metabolomics
UPLC-MS/MS

Genomics

544 endogenous metabolites

4,795 AMD SNPs
Methods

• Association between known AMD SNPs and plasma metabolites
  • Linear regression models adjusted for age, sex, smoking, 10 metabolite principal components (PCs) and 10 SNP PCs and accounting for false discovery rate
  • First for each cohort and then combined by meta-analysis
Results

ASPM

3 mQTL
q-value< 2.24x10^{-2}

2-hydroxy-3-methylvalerate

Amino Acid
Leucine, Isoleucine, Valine

LIPC

25 mQTL
q-value< 1.14x10^{-2}

1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)
1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)
1-oleoyl-2-linoleoyl-GPE (18:1/18:2)*

Lipids
Phosphatidylethanolamines (PE)
Discussion

• *LIPC* gene with highest number of highly significant mQTL
Limitations

• Relatively small sample size
• Cross-sectional design
Summary

• AMD risk SNPs have an impact on the plasma metabolome
• Genetic-metabolomic associations can provide unique insights into the pathogenesis of AMD
• Highest number of associations were seen with *LIPC* polymorphisms, which were associated with glycerophospholipid metabolites
• *LIPC* gene and glycerophospholipids pathway are likely crucial in AMD pathogenesis and may represent potential targets for treatment of AMD
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